Amendments to the Drawing Figures:

Fig. 2A: A typographical error in Fig. 2A is corrected, where the incorrect word "leather(!?)" is changed to 'leaflet', as described on page 10, paragraph [0040]. A replacement drawing sheet identified as "Replacement Sheet" is enclosed herewith.

REMARKS

This paper is in response to the Office communication mailed November 18, 2004.

I. Amendments

Claims 1 and 19 are amended to recite that the method includes incubating the particles "in a medium" and under conditions effective to remove the charged lipid from the external lipid leaflet "into the medium." Basis is on page 17, paragraph [0060] ("Removal of the charged lipids from the outer lipid coating.....is achieved by placing the lipid particles in a medium into which the charged lipids partition.")

New claims 22 and 23 recite that the method further includes separating the lipid particles from said medium. Basis is on page 18, paragraph [0063] ("After incubation, the lipid particles.....were isolated from the other lipid components in the incubation medium by....); page 19, paragraph [0065] ("The asymmetric lipid particles were separated from the other lipid vesicles in the incubation medium using...."); page 31, paragraph [0091] ("After the completing of the incubation, the sink liposomes were then separated by ....").

Typographical errors in the specification have been corrected.

A typographical error in Fig. 2A is corrected. A Replacement drawing sheet is enclosed.

II. Response to Election/Restrictions

Claims 1-22 are restricted into Group I (claims 1-12 and 19-22) and Group II (claims 13-18). Applicants confirm election of Group I for prosecution, without traverse. Claims 13-18 stand canceled, accordingly.

III. Rejection Under 35 U.S.C. § 102

Claims 1-4, 6-8, 11, 12, 19, and 22 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Sempel *et al.*, U.S. Patent No. 6,287,591. This rejection is respectfully traversed for the following reasons.

A. The Present Invention

Claim 1 as amended relates to a method of preparing lipid particles. The method involves preparing the particles from a charged lipid, where the particles have an outer lipid coating that includes an external lipid leaflet. The particles are then incubated in a medium and under conditions effective to remove charged lipids from the external lipid leaflet into the incubation medium.

B. The Applied Art

SEMPLE *ET AL*. describe a method of making lipid particles comprising an entrapped agent. The lipid particles are made from two lipid components, a first lipid and a second lipid. The first lipid component containing a protonatable group that has a pKa such that as the lipid is in a charged from at a first pH and a neutral form at a second pH (Col. 3, lines 30-46). The second lipid component is a lipid that prevents particle aggregation (Col. 3, lines 52-55). The two lipid components and a therapeutic agent are mixed together in a buffer to form an "intermediate mixture" (Col. 3, lines 33-37) comprised of lipid-encapsulated therapeutic particles. Next, the pH of the intermediate mixture is changed to neutralize at least some of the exterior surface charges on the lipid particles (Col. 3, lines 38-44).

C. Analysis

The standard for lack of novelty, that is, for anticipation, is one of strict identity. To anticipate a claim for a patent, a single prior source must contain all its essential elements. M.P.E.P. § 2131.

The claimed method includes preparing lipid particles containing a charged lipid and a therapeutic agent, and then incubating the particles under conditions to *remove the charged lipid* from the external lipid leaflet of the particle.

In contrast, Semple *et al.* describe a method where the lipid particles containing a charged lipid are incubated under conditions, i.e., a change in pH, that cause the charged lipid to de-protonate, i.e, become neutral. Nowhere does Semple *et al.* teach removing the charged lipid from the particle.

The Examiner's summary of applicants method set forth on page 6 of the Office action (lines 3-5) incorrectly characterizes the claimed method in reciting "incubating the lipid particles under conditions to remove the charge from the external lipid leaflet." Claim 1 recites that the incubating step removes the charged lipid from the external lipid leaflet.

Also, on page 7, lines 5-8 the Examiner states that "Since the method neutralizes charges on the exterior surface of the lipid, the lipid particle produced reads on an asymmetric charged lipid composition." The Examiner is reminded that the instant claims are to a method of preparation, and not to a lipid composition.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102.

V. Rejection under 35 U.S.C. § 103

Claims 1-5, 6-8, 11, 12, 19, and 22 were rejected under 35 U.S.C. §103 as allegedly obvious over Semple *et al.*, U.S. Patent No. 6,287,591, in view of Tardi *et al.*, US 2003/0091621). This rejection is respectfully traversed for the following reasons.

A. The Present Invention

The present invention is summarized above.

B. The Applied Art

SEMPLE *ET AL*. are summarized above.

TARDI *ET AL*. describe a method of loading an agent into a liposome by preparing a liposome containing an encapsulated metal and then adding an agent to be loaded to the external liposome suspension medium ([0011], [0032],

[00139]). The agent is then taken up into the liposomes ([00157]) during incubation of the mixture.

C. Analysis

According to the M.P.E.P. § 2143.03, "to establish a prima facie case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. All words in a claim must be considered in judging the patentability of that claim against the prior art." [citations omitted].

Present claims 1 and 19 describe a method of preparing lipid particles by (i) preparing lipid particles from a charged lipid, where the particles have an outer lipid coating that includes an external lipid leaflet and then (ii) incubating the particles in a medium and under conditions effective to remove charged lipids from the external lipid leaflet into the incubation medium.

Semple *et al.* fail to show or suggest incubation of lipid particles under conditions effective to removed charged lipids from the external lipid leaflet of the particles. In Semple *et al.*, the medium in which the lipid particles are suspended is treated to undergo a change in pH, so that the lipids lose their charge. Nowhere does Semple *et al.* show or suggest incubating to remove the charged lipids from the particles.

The teaching of Tardi *et al.* does correct this deficiency in Semple *et* al. In Tardi *et* al., there is simply no teaching of incubating liposomes to remove a charged lipid from the external bilayer leaflet.

The Examiner asserts it would be obvious to modify the teachings of Semple *et al.* to add the lipid-polymer-ligand conjugate taught in Tardi *et al.* (paragraph [0080]). Even if the lipid-polymer-ligand conjugate of Tardi *et al.* was combined with the teaching of Semple *et al.*, the combination does not arrive at the method of claim 1 or claim 19, or even of claim 5. First, the combined teachings fail to show or suggest incubating liposomes to remove a charged lipid from the external bilayer leaflet. Second, in both Semple *et al.* and Tardi *et al.* lipid particles or liposomes are made by preparing a lipid mixture (i.e., a first lipid,

a second lipid, and, in some embodiments, a lipid-polymer-ligand conjugate) that is hydrated to form lipid particles or liposomes (see [0078] of Tardi *et al.*; see Col. 3, lines 33-37of Semple *et al.*). Thus, the combined teaching of Semple, *et al.* and Tardi *et al.* provides for a lipid mixture, which can optionally include a lipid-polymer-ligand conjugate, that is hydrated to form lipid particles. In contrast, the present claims recite incubating the lipid particles (i.e., preformed lipid particles) in a medium that contains the lipid-polymer-ligand conjugate. Thus, the combined teachings fail to show or suggest the present invention.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103.

VI. Conclusion

If the Examiner has any questions or believes a telephone conference would expedite prosecution of this application, the Examiner is encouraged to call the undersigned at (650) 564-2867.

Respectfully submitted,

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